APIXABAN (ELIQUIS®)

Thrombosis Canada
Thrombose Canada

OBJECTIVE:

To provide an overview of the mechanism of action, licensed indications, dosing regimens, and side-effect profile of apixaban.

MECHANISM OF ACTION:

Apixaban is an oral factor Xa inhibitor. By binding reversibly to the active site of factor Xa, apixaban attenuates thrombin generation and reduces fibrin formation.

INDICATIONS:

Apixaban is currently licensed in Canada for:

- Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation
- Treatment of venous thromboembolic events, including deep vein thrombosis (DVT) and pulmonary embolism (PE) and prevention of recurrent DVT and PE
- Prevention of DVT and PE after elective hip or knee replacement surgery.

DOSING:

- **Prevention of stroke and systemic embolism in atrial fibrillation**: 5 mg BID. No dose adjustment is generally necessary in patients with mild or moderate renal impairment or in those with CrCl 25-30 mL/min. However, a reduced dose of 2.5 mg BID is advised in patients with at least two of the following: (1) serum creatinine ≥ 133 µmol/L, (2) age ≥80 years, or (3) body weight ≤60 kg. Data are limited in patients with a CrCl of 15-24 mL/min and no dosing recommendation is provided by the manufacturer. Apixaban is not recommended in patients with CrCl <15mL/min or for those undergoing dialysis.
- **Acute treatment of DVT or PE:** 10 mg BID for 7 days, followed by 5 mg BID. No dose adjustment is necessary in patients with mild or moderate renal impairment (CrCl ≥30 mL/min). There are limited clinical data in patients with severe renal impairment (CrCl 15-29 mL/min) and apixaban should be used with caution in these patients because of a potentially higher bleeding risk. Apixaban is not recommended in patients with CrCl <15 mL/min or for those undergoing dialysis.
- **Continued prevention of recurrent DVT and PE:** After at least 6 months of treatment, consideration can be given to reducing the dose to 2.5 mg PO BID for long-term prevention of recurrent VTE.
- **Thromboprophylaxis after hip/knee arthroplasty**: 2.5 mg BID starting 12-24 hours after surgery and continuing for 14 or 35 days after knee or hip replacement, respectively.

MONITORING:

Routine laboratory coagulation monitoring is not necessary. The prothrombin time/international normalized ratio (PT/INR) and activated partial thromboplastin time (aPTT) are often normal in patients taking apixaban and do not provide reliable measures of the anticoagulant activity. Specific anti-factor Xa assays using apixaban calibrators are available in some laboratories to determine the plasma concentration but are not validated across centres and "safe" or therapeutic levels have not been established. For more details about specific testing, see the **Clinical Guide: DOACs: Coagulation Tests**.

Although routine laboratory coagulation monitoring is not required for long-term apixaban use, periodic clinical assessment is important to determine and reinforce compliance, review comorbidity and medication changes, including an assessment for possible interacting agents, and provide education. Furthermore, for most patients, at least yearly assessment of creatinine clearance is recommended. The creatinine should be measured more frequently in patients with an abnormal value at baseline or at risk of worsening renal function. [See Clinical Resource: **Direct Oral Anticoagulant (DOAC) Follow-Up Checklist for Clinicians; Direct Oral Anticoagulation (DOAC) Monitoring Checklist for Pharmacists**]

ADVERSE EFFECTS:

The major adverse effect of apixaban is bleeding; concomitant use of antiplatelet drugs or other anticoagulants increases the bleeding risk. Apixaban should be avoided in patients with indwelling epidural catheters or with a history of recent spinal puncture in order to reduce the risk of epidural or spinal hematomas. Drug levels can also be increased or decreased by the use of concomitant medications (see Drug interactions). Approaches to the management of bleeding can be found in the **Clinical Guide: DOACs: Management of Bleeding** and the **Tool: Bleed Management**.

PERI-PROCEDURAL MANAGEMENT:

See the **Clinical Guide: NOACs/DOACs: Peri-operative Management** and the **Tool: Perioperative Anticoagulant Management.**

SPECIAL CONSIDERATIONS:

Administration: Apixaban may be taken with or without food.

Pregnancy and breast feeding: Apixaban crosses the placenta and should not be used in pregnancy. It should also be avoided in nursing mothers because it is uncertain whether apixaban appears in the breast milk.

Renal and hepatic dysfunction: Apixaban is not recommended in patients with CrCl <15 mL/min and those undergoing dialysis. Dosing recommendations by clinical indication for patients with less severe renal dysfunction are described above under Dosing. Apixaban should be used with caution in those with mild or moderate or hepatic impairment (Child-Pugh class A or B); however, no

dosing modification is recommended in these patients. Apixaban is not recommended in patients with severe hepatic impairment (Child-Pugh class C) and is contraindicated in patients with coagulopathy associated with hepatic disease.

Drug interactions: The concomitant use of apixaban and drugs and/or herbal products that inhibit or induce both P-glycoprotein (P-gp) and CYP3A4 should be avoided. Patients taking strong inhibitors of both CYP3A4 and P-gp are at an increased risk of bleeding. Examples of inhibitors include azole antifungals (e.g. itraconazole, ketoconazole, voriconazole, and posaconazole), macrolide antibiotics (e.g. clarithromycin, erythromycin) and HIV protease inhibitors (e.g. ritanovir). Alternatively, concomitant use of strong inducers (e.g. rifampin, carbamazepine, phenytoin, St. John's Wort) can reduce apixaban levels.

Reversal: Andexanet alfa, a recombinant modified human factor Xa decoy protein, has been shown to reverse inhibition of factor Xa by apixaban and rivaroxaban in healthy volunteers and in those with major bleeding. In the latter group, effective hemostasis was noted at 12 hours in 79% of patients; however, thrombotic events occurred in 18% (12/67) of patients during 30-day follow-up. This agent is not yet available for use in Canada, although it has acquired FDA approval. Clinicians should consult their local institutional protocols for use of indirect reversal agents such as prothrombin complex concentrates (PCC) when reversal of apixaban is indicated for major or life-threatening bleeding. Approaches to the management of bleeding can be found in the **Clinical Guide: DOACs: Management of Bleeding** and the **Tool: Bleed Management**.

Pediatrics: Apixaban is not recommended for use in children until ongoing studies establish the pharmacokinetics, pharmacodynamics, safety, and efficacy of apixaban in these patients.

Treatment of cancer-associated thrombosis: Apixaban does not currently have a licensed indication in Canada specifically for use in this patient population but a randomized trial comparing apixaban (10 mg twice daily for 7 days then 5 mg twice daily) and subcutaneous dalteparin (at a dose of 200 IU/kg once daily for the first month, followed by 150 IU/kg once daily) for 6 months showed that, in this study population, apixaban was non-inferior to low molecular weight heparin (LMWH) in terms of both recurrent venous thromboembolism and major bleeding. The latter contrasts with other studies, which reported a higher incidence of major bleeding with other direct oral anticoagulants than with dalteparin in a similar population. Episodes of nonmajor bleeding were numerically higher in the apixaban group, a similar finding to that in studies of other direct oral anticoagulants. See the **Clinical Guide: Cancer and Thrombosis**.

Primary thrombosis prophylaxis in ambulatory cancer patients: When given in doses of 2.5 mg orally twice daily in ambulatory cancer patients judged to be at intermediate or high risk for venous thromboembolism according to their Khorana score, apixaban was associated with a reduction in overall (symptomatic and incidental) thrombosis risk from 10.2% to 4.2% (Hazard ratio [HR] of 0.41; 95% confidence interval (CI) 0.26-0.65); however, this came at a cost of increased major bleeding risk from 1.8% to 3.5% (HR 2.95; 95% CI, 1.01-3.95). As a result, decisions regarding the use of apixaban for primary prophylaxis in ambulatory cancer patients will need to be individualized and take into account estimated venous thromboembolism risk, cancer site (major

bleeds were more likely to be gastrointestinal, genitourinary, or gynecologic in nature), patient values and preferences, and impact of drug cost. Apixaban is not currently licensed for this indication in Canada. See the **Clinical Guide: Cancer and Thrombosis**.

Atrial fibrillation patients receiving $P2Y_{12}$ inhibitor for recent acute coronary artery syndrome (ACS) or percutaneous coronary intervention (PCI): The AUGUSTUS trial suggested that in atrial fibrillation patients with recent ACS or PCI taking a $P2Y_{12}$ inhibitor, apixaban (at stroke prevention doses) without Aspirin resulted in less bleeding and fewer hospitalizations (without significant differences in the incidence of ischemic events) as regimens that included a vitamin K antagonist, Aspirin, or both.

OTHER RELEVANT THROMBOSIS CANADA CLINICAL GUIDES, RESOURCES AND TOOLS:

- Cancer and Thrombosis
- DOACs: Coagulation Tests
- DOACs: Comparison and Frequently Asked Questions
- DOACs: Management of Bleeding
- DOACs: Perioperative Management
- Stroke Prevention in Atrial Fibrillation
- Thromboprophylaxis: Orthopedic Surgery
- Clinical Resource: Direct Oral Anticoagulant (DOAC) Follow-Up Checklist for Clinicians
- Clinical Resource: Direct Oral Anticoagulant (DOAC) Monitoring Checklist for Pharmacists
- Tool: Perioperative Anticoagulant Management Algorithm
- Tool: Bleed Management

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